Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis

Mineralocorticoid Receptor Antagonists in Elderly patients with Heart Failure: A Systematic Review and Meta-analysis.

Keywords: mineralocorticoid receptor antagonist, aldosterone, heart failure, left ventricular dysfunction, elderly.

Word Count: 2974 words

ABSTRACT

Background: Mineralocorticoid receptor antagonists (MRAs) improve outcomes in several populations of patients with heart failure (HF) but there has been no systematic review of MRAs in older patients.

Objectives: Systematic review and meta-analysis of the efficacy and safety of MRA treatment in elderly HF patients.

Data sources: Trials were identified through a literature search until January 24th 2015.

Study selection: Randomised control trials (RCTs) of MRAs in patients with HF and/or left ventricular systolic dysfunction aged ≥65 years; or with sub-group analysis of patients ≥65 years; or with mean participant age ≥70 years.

Data extraction and synthesis: Efficacy outcomes were mortality, hospitalisation for cardiovascular causes, symptom status or functional capacity. Safety outcomes were hyperkalaemia and renal dysfunction. Data were analysed using relative risk ratios with 95% confidence intervals. Relative risk ratios were pooled where more than three estimates were available.

Results: Seven RCTs were included (total n=8638). Three RCTs in HF with reduced ejection fraction (HEFREF) reported overall benefit from MRA therapy with no significant treatment interaction for age; the effects of MRAs on mortality in patients ≥75 years displayed marked inter-study heterogeneity. In four RCTs of HF with preserved ejection fraction (HEFPEF), MRA treatment had no significant effect on any efficacy outcome.

Conclusions: MRAs improve clinical outcomes in selected cohorts of older patients with HEFREF but not HEFPEF. In patients ≥75 years with HEFREF, the effect of MRA treatment on overall mortality is uncertain. Further study is required in subgroups of elderly patients with both HEFREF and HEFPEF.

249 words

Introduction

Heart failure (HF) is an increasing global public health problem that results in premature mortality, recurrent hospitalisation and debilitating symptoms and imposes a huge economic burden on healthcare resources.[1] Increasingly, HF represents a disease of older people with a population prevalence of 9-10% in individuals aged 75-84, and 17-18% in those 85 and older, compared with <1% in patients <65 years.[2] Within the UK, the median age of patients hospitalised with HF is now 80 years.[3]

Despite major advances in evidence-based treatments for HF with reduced ejection fraction (HEFREF), older patients remain under-represented in clinical trials and have substantially worse outcomes than younger patients.[4-6] Age related physiological changes, comorbidity, frailty, polypharmacy and altered drug pharmacokinetics may all attenuate the potential benefit from drug therapy in elderly HF patients and increase the risk of side effects and complications.[7] Moreover, the prevalence of HF with preserved ejection fraction (HEFPEF), a condition with a lack of proven therapies, is proportionately far greater in the elderly HF population.[6, 8-9] It is therefore essential to know whether recommended treatments are efficacious and safe for older people.

Mineralcorticoid receptor antagonists (MRAs) have been shown to reduce mortality and hospitalisation in several cohorts of patients with HEFREF[12-14] and have recently been tested in patients with HEFPEF.[15,16] To date there has been no dedicated systematic review of the effects of MRA treatment in older patients with HF. We therefore sought to clarify the efficacy and safety of MRAs in older HF patients with both reduced and preserved ejection fraction.

Methods

Search Strategy and Selection Criteria

We performed a systematic review, and report it using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[17] Retrieved results were filtered to include randomised controlled trials (RCTs) that fulfilled one or more of the following conditions: i) enrolled only patients aged ≥65 years, ii) included sub-group analysis of patients aged ≥65 years or iii) had a mean participant age of ≥70 years. The drugs of interest were spironolactone, epleronone and canrenone. Trials were required to include patients with HF of any aetiology and/or left ventricular systolic dysfunction (LV ejection fraction <40%) and to report at least one relevant clinical efficacy or safety outcome. The primary efficacy outcome was all cause mortality. Secondary efficacy outcomes were cardiovascular mortality, hospitalisation for cardiovascular causes, symptom status (validated quality of life assessment tools, New York Heart Association (NYHA) class), or functional capacity (6 minute walk test, VO_2 max). Safety outcomes were hyperkalaemia and renal dysfunction, defined as per the primary trial publication.

Data source and Study Search

The following databases were searched MEDLINE (Ovid platform 1946 to January 24th 2015); EMBASE (Ovid platform 1980 to January 24th 2015); and CINAHL (Ebsco platform 1937 to January 24th 2015). Reference lists of the included RCTs and identified review articles were hand searched to find other potentially eligible studies. To ensure a large safety net, a sensitive search strategy was employed. We searched using a combination of MeSH headings and keywords (and their derivatives): mineralocorticoid receptor antagonist, aldosterone antagonist, spironolactone, epleronone, canrenone, heart failure, ventricular dysfunction (see also Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). No language restrictions were applied. We searched for grey literature using Google and Google Scholar and also specifically searched for the drugs of interest on the websites of the United States Food and Drug Administration, other European and international health

regulatory authorities. We searched clinical trials registers (https://clinicaltrials.gov; www.clinicaltrialsregister.eu) for ongoing and unpublished trials.

The search of electronic databases was conducted by two independent reviewers who identified potentially relevant articles based on title or title and abstract. Full text articles were then retrieved for further assessment to determine whether they met inclusion criteria. Discrepancies were resolved by consensus.

Quality Assessment and Data Extraction

Relevant data were extracted and entered into a data collection form. Where available, outcomes data were extracted specifically for 'younger elderly' (65-74 years) and 'older elderly' (≥75 years) patients, as well as for patients with HEFREF and HEFPEF. Studies were assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[18], with scoring performed by two independent authors and differences resolved by consensus.

This systematic review was registered with PROSPERO, the international prospective register of systematic reviews (registration number CRD42013004478).

Data synthesis and analysis

Relative risk ratios were pooled where more than three estimates were available. Most studies reported hazards ratios. Some studies only provided proportional data and in these cases we calculated relative risk estimates derived from two by two contingency tables. We assumed that the 'true effect' estimate would be the same across all studies and initially derived overall pooled estimates using a fixed-effects model. In those meta-estimates where there was a high degree of heterogeneity (I^2> 30%) we also provided estimates derived from a random effects model. Treatment effects and derived meta-estimates are

expressed as risk ratios ± 95% confidence intervals. Continuous variables, unless otherwise stated, were expressed as mean± SD. Meta-analysis was performed using RevMan 5.3 software (The Cochrane Collaboration, Oxford, UK)

Results

One thousand eight hundred and sixty four articles were identified by the initial search strategy and, of these, eight articles[12-16, 19-21] describing seven RCTs were included in the final review (Figure 1). A subgroup study of the EMPHASIS-HF high risk[19] reported a prespecified analysis of efficacy and safety outcomes in trial patients ≥75 years. The original trial publication[14] included a subgroup analysis for the primary outcome in patients ≥65 years and was therefore also included. Study characteristics and quality are shown in table 1. Quality was generally moderate or high and with one exception[20] the studies were double-blinded and placebo-controlled with sample size based on appropriate power calculations. Overall dropout rates were <20% in all but one[12] of the studies whilst the differential dropout rate between the two treatment arms was <10% in all. One trial included a prespecified subgroup study in patients ≥75 years[19] but otherwise, the studies containing subgroup analysis of older patients offered limited characterisation and outcome data specific to our population of interest; consequently, for the purposes of this review, their quality was graded as moderate. A comprehensive search of grey literature and regulatory health websites uncovered additional relevant data for three of the included RCTs (see Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/).

Efficacy Outcomes

HEFREF

Three trials in patients with HEFREF reported relevant mortality and hospitalisation outcomes (Table 1, Figure 2). All reported an overall benefit from MRA therapy with respect to the individual trial's primary endpoint with no significant treatment interaction for age (Table 1). As shown in Figure 2, the magnitude of treatment effect for these endpoints in older patients was broadly similar to that in younger patients. The major exception to this was in patients ≥75 years with post-MI HEFREF; in these patients there was no apparent benefit from eplerenone treatment for either of the two co-primary endopoints, however age

≥75 years was not examined as a treatment interaction term. Additionally, in patients ≥75 years with stable NYHA class II HEFREF, the effect of eplerenone on the trial's primary composite endpoint was driven entirely by a reduction in hospitalisation for HF with no difference in CV mortality between the two treatment arms.

Even if not reported as primary endpoint we found data on all cause mortality data in patients ≥75 and <75 years for all three HEFREF trials (Figure 3). In patients <75 years there was a substantial and highly significant reduction in mortality that was consistent across studies (OR 0.74; CI 0.66-0.83; P<0.00001; I^2 = 5%). In contrast, in patients ≥75 years, we observed marked heterogeneity between studies (I^2 = 79%; P = 0.009). On a random effects model there was no significant reduction in mortality in this elderly population with MRA therapy (OR 0.8; CI 0.52-1.25; P = 0.33).

Specific hospitalisation data for elderly patients was obtained for only one of the HEFREF studies.[19] Although not a prespecified analysis, eplerenone significantly reduced hospitalisation for HF (Figure 2) and for cardiovascular causes (HR 0.62; CI 0.47-0.82) in patients ≥75 years with chronic stable HEFREF and NYHA class II symptoms.

We found no data on the effects of MRA treatment on quality of life and/or functional capacity outcomes in older patients with HEFREF.

HEFPEF

In the single trial of patients with HEFPEF that reported mortality and hospitalisation outcomes, MRA therapy did not significantly reduce the incidence of the individual trial's primary composite outcome Table 1; Figure 2). Hazard ratios for older patients were similar to those of the overall trial population and there was no significant treatment interaction for age.

Three RCTs, all in patients with HEFPEF, reported limited quality of life and/or functional capacity outcomes (Table 1) in older patients. No significant treatment effects were observed for any of these outcomes.

Safety Outcomes

Our specified safety endpoints were obtained from three studies (please see the table Appendix 3 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). In two large trials, the incidence of hyperkalaemia (K+≥5.5 mmol/L) in patients ≥75 years was increased by MRA treatment. However, further data from one of these trials and a small trial of patients with mean age 71 years suggested a low overall incidence of severe hyperkalaemia (K^+≥6.0) or hospitalisation for hyperkalaemia with no significant difference in the frequency of these events between the two treatment arms. In one large trial, neither decline in eGFR from baseline nor incidence of hospitalisation for worsening renal function was increased by MRA treatment.

Discussion

This systematic review of MRA treatment in older patients with heart failure included seven RCTs with a total of 8,638 patients aged ≥65 years and >3,300 aged ≥75 years. Across the spectrum of HEFREF, we found no overall mortality benefit from MRA therapy in patients ≥75 years, however MRAs did improve clinical outcomes (mortality and/or hospitalisations) in older patients with chronic stable HEFREF and in younger elderly patients with post-MI LVSD. There was no evidence of benefit from MRA treatment in elderly patients with HEFPEF.

An age threshold of 65 years is frequently used to define elderly patients in both clinical and research settings. This cutoff may no longer be appropriate in conditions such as heart failure where the vast

majority of patients are >65 years. In contemporary population-based studies, the mean age of patients with HF is now 80 years;[22] by comparison, the mean age of participants among large RCTs included in this review ranged from 64 to 68 years and patients ≥75 years contributed less than one third of the combined trial population. Moreover, whilst other established therapies for HF including ACE inhibitors and beta-blockers appear to be beneficial in 'younger' elderly patients there is some evidence to suggest they are less effective in patients ≥75 years.[23-24] We therefore sought relevant outcomes data for patients ≥75 years as well as for all patients ≥65 years.

Across three large RCTs of MRAs in distinctive HEFREF populations, we observed a consistent mortality reduction in patients <75 years. In the two trials for which data were available, treatment response in patients aged 65-74 years closely mirrored that of younger patients. In contrast, the effect of MRAs on mortality in older elderly patients displayed marked heterogeneity. In chronic stable HEFREF, MRA treatment caused a striking reduction in all-cause death in patients ≥75 years with NYHA class III-IV symptoms. We were unable to ascertain the mode of death among specific age cohorts, however within the overall trial population, MRAs reduced both sudden death and death from progressive heart failure. In a subsequent trial in NYHA class II patients, MRA therapy had a neutral effect on mortality among patients ≥75 years but reduced hospitalisations for heart failure by over 40% This suggests that MRA treatment may serve to retard progression of heart failure in older patients with possible mechanisms including prevention of myocardial fibrosis and reduced sodium retention.[25] In contrast to chronic stable HEFREF, neither all-cause mortality nor the composite of CV mortality or CV hospitalisation was reduced by MRA treatment in patients ≥75 years with early post-MI LVSD.

The above data suggest that the response to MRAs among the older elderly with HEFREF may depend upon the particular patient subtype. However, we were unable to explore several other potential sources for the observed variation in treatment effect. The three trials included in our meta-analysis, spanned a recruitment period of 15 years, during which time background drug and device therapy underwent

considerable change. Indeed, the background use of beta-blockers in the trials varied from 10%[12] to 87%.[14] The trials also employed two different investigational drugs (spironolactone and eplerenone) and had populations that differed with respect to comorbidities, LV ejection fraction and aetiology of LVSD. Compounding this, the baseline characteristics of elderly patients were available for only one of the studies. We therefore call for an individual patient data meta-analysis of these RCTs to further explore the sources of heterogeneity in treatment response to MRAs among the very elderly, as well as to clarify the effects in elderly patients <75 years and to evaluate other major outcomes of interest in elderly patients. Beyond this, subgroup analysis from the forthcoming trial of early post-MI spironolactone treatment [Aldosterone Blockade Early After Acute Myocardial Infarction, ALBATROSS, NCT01059136] may provide further insights into the utility of MRAs in very elderly patients with post-MI LVSD.

No treatments have yet been convincingly shown to improve outcomes in HEFPEF, the predominant form of HF among older patients.[6, 26]. One large RCT with subgroup analysis in elderly patients reported the effects of MRA therapy on major clinical outcomes in HEFPEF.[16] Whilst MRA treatment did not reduce the primary composite outcome within the overall study population, interpretation of the results has been complicated by marked geographical variation with respect to both patient profile and treatment effect[27]. No such variation in response to treatment was observed by patient age and outcomes in both the very elderly and younger elderly patients appeared similar to those of non-elderly patients. We found limited data regarding the effects of MRAs on other efficacy outcomes in elderly HEFPEF patients however two trials showed no apparent benefit on exercise capacity. Further work is now required to determine whether distinct subpopulations of elderly patients with HEFPEF may derive benefit from MRA therapy. Future studies should ideally include more robust assessments of symptoms, functional capacity and quality of life in addition to mortality and hospitalisation outcomes.

The available safety data in this review confirms an increased risk of hyperkalaemia with MRA treatment in patients ≥75 years. However, in the single large RCT for which comprehensive safety data were available, the rates of severe hyperkalaemia, hyperkalaemia requiring hospitalisation or hospitalisation for worsening renal function were all very low and did not differ from elderly patients in the placebo arm. Registry studies comprising real world patients have reported considerably higher rates of serious safety outcomes with MRA treatment in the elderly, particularly hyperkalaemia.[28-29] This may in part be explained by more indiscriminate use of MRAs in everyday clinical practice among patients at risk of complications. Indeed more than 30% of Medicare beneficiaries prescribed spironolactone shortly after the publication of the Randomised Aldactone Evaluation Study (RALES) would have been ineligible for inclusion in RALES on account of baseline renal function or serum potassium.[29] Whilst such real world studies reinforce the need for caution when prescribing MRAs to older patients, the limited data in this review, suggests that the risks of serious complications can be mitigated through careful patient selection, monitoring and dose adjustment. Future studies with large elderly representation should consider additional safety endpoints relevant to older people such as the incidence of falls, fractures or cognitive deterioration.

Study Limitations

The number of studies identified was relatively small and we are unable to exclude the possibility of publication bias. Furthermore, the original trial publications relating to these studies contained very limited data specific to elderly patients and we had no access to the primary trial data. Much of the data included in the review was, therefore previously unpublished and obtained from formal assessments by regulatory health authorities available on publically accessible websites. Whilst this may also be viewed as a strength of our search process, the results obtained were unavoidably sparse and, in several areas, incomplete. This could be addressed by future individual patient data meta-analysis of the major MRA RCTs in HEFREF as well as further dedicated study of MRAs in specific elderly HF cohorts.

We found little evidence for the effects of MRAs on efficacy outcomes other than mortality, particularly in the setting of HEFREF. The absence of robust evidence for outcomes such as quality of life and symptom status is disappointing as their importance, relative to mortality, is likely to increase with advancing age. We urge greater inclusion of these endpoints in subsequent trials, particularly those with major elderly representation. All of the included studies used either spironolactone or eplerenone. Further work is required to evaluate the effects of canrenone and the novel, non-steroidal MRA, finrenone, in older heart failure patients.

The literature under-represents the main population of older people with HF, mostly in their 80s and 90s. The presence of certain comorbid conditions such as diabetes, chronic kidney disease and chronic obstructive pulmonary were frequently reported, however other comorbidities such as cognitive impairment were not routinely recorded and none of the studies undertook a formal assessment of frailty.

Conclusions

The effect of MRAs on all cause mortality in older patients is uncertain, but they improve several major clinical outcomes in older patients with chronic HEFREF and in those aged <75 years with post-MI LVSD. In contrast, there is no evidence to support MRA treatment in older patients with HEFPEF. Whilst MRAs increase the risk of mild hyperkalaemia, limited data do not suggest major safety concerns in carefully selected and monitored elderly patients. Further study, with efficacy and safety outcomes relevant to older people, is required, particularly the very elderly.

Conflicts of interest

None declared.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.
2. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. 2004 Eur Heart J. 2004;25(18):1614-9.
3. National Institute for Cardiovascular Outcomes Research. National Heart Failure Audit 2012 – 2013. www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/hfannual12-13.pdf
4. Tuppin P, Cuerq A, de Peretti C, et al. Two-year outcome of patients after a first hospitalization for heart failure: A national observational study. Arch Cardiovasc Dis. 2014;107(3):158-68.
5. Herrera A, Snipes S, King D, et al. Disparate Inclusion of Older Adults in Clinical Trials: Priorities and Opportunities for Policy and Practice Change. Am J Public Health. 2010;100(Suppl1):S105–S112. doi:10.2105/AJPH.2009.162982
6. Mogensen UM, Ersbøll M, Andersen M, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J Heart Fail. 2011;13(11):1216-23.
7. Lazzarini V, Mentz RJ, Fiuzat M, et al. Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail. 2013;15(7):717-23.
8. Owan T.E., Hodge D.O., Herges R.M., Jacobsen S.J., Roger V.L., Redfield M.M.; Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-259.
9. Kitzman D.W., Gardin J.M., Gottdiener J.S., et al;for the Cardiovascular Health Study Group Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol. 2001;87:413-419.
10. Struthers AD, MacDonald TM. Review of aldosterone- and angiotensin II-induced target organ damage and prevention. Cardiovasc Res 2004;61:663–670.

11. Edelmann F, Tomaschitz A, Wachter R, et al. Serum aldosterone and its relationship to left ventricular structure and geometry in patients with preserved left ventricular ejection fraction. Eur Heart J. 2012;33(2):203-212.
12. Pitt B, Zannad F, Remme W, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med 1999;341:709-717.
13. Pitt B, Remme W, Zannad F, et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. N Engl J Med 2003;348:1309-1321.
14. Zannad F, McMurray J, Krum H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med 2011;364:11-21.
15. Pitt B, Pfeffer M, Assmann S, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383-92.
16. Edelmann F, Wachter R, Schmidt A, et al. Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction. The Aldo-DHF Randomized Controlled Trial. JAMA. 2013;309(8):781-791.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
18. Schunemann A, Oxman A, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106.
19. Eschalier R, McMurray J, Swedberg K, et al. Safety and Efficacy of Eplerenone in Patients at High Risk for Hyperkalemia and/or Worsening Renal Function. Analyses of the EMPHASIS-HF Study Subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol 2013;62:1585–93.
20. Mak G, Ledwidge M, Watson C, et al. Natural History of Markers of Collagen Turnover in Patients With Early Diastolic Dysfunction and Impact of Eplerenone. J Am Coll Cardiol 2009;54:1674–82.
21. Kurrelmeyer K, Ashton Y, Nagueh S, et al. Effects of spironolactone treatment in elderly women

with heart failure and preserved left ventricular ejection fraction. J Card Fail. 2014;20(8):560-8.

22. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–1402.
23. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26:215–225.
24. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000; 355:1575–1581.
25. Zannad F, Alla F, Dousset B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). Circulation 2000;102:2700-6.
26. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725 – 2736.
27. Pfeffer MA, Claggett, B, Assmann SF, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015; 131(1):34-42
28. Hernandez AF1, Mi X, Hammill BG, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. JAMA. 2012;308(20):2097-107
29. Masoudi FA, Gross CP, Wang Y, et al. Adoption of spironolactone therapy for older patients with heart failure and left ventricular systolic dysfunction in the United States, 1998–2001. Circulation. 2005;112:39–47.

Figures

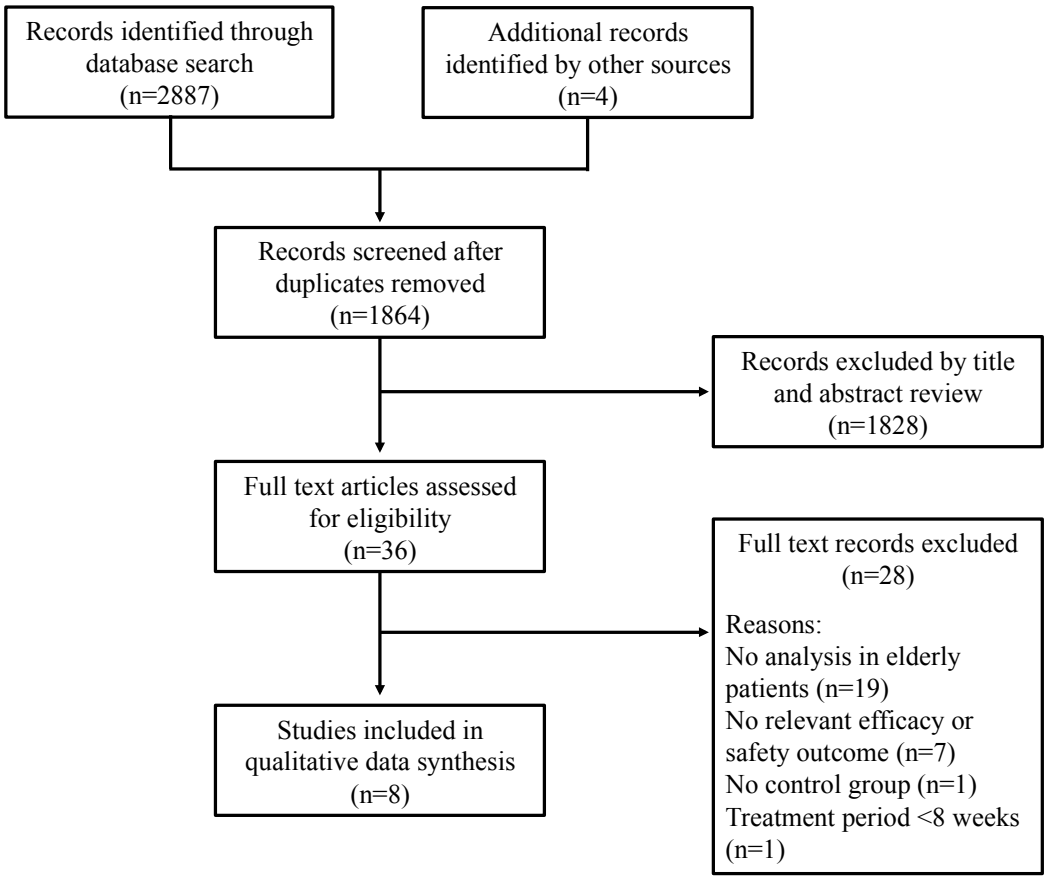

Figure 1. PRISMA flowchart of search strategy and study selection.

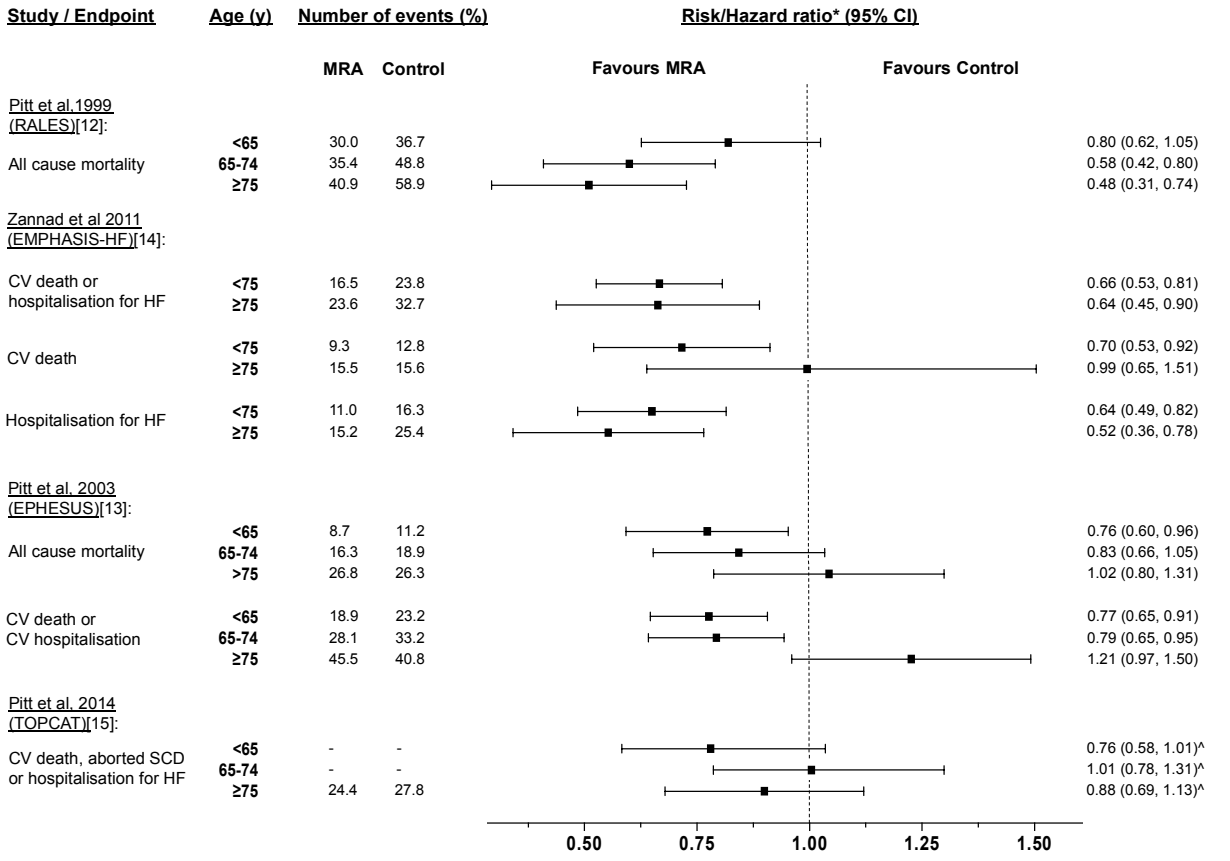

Figure 2. Absolute events and Risk/Hazard ratios for relevant mortality and hospitalisation endpoints.

*Unless otherwise stated, data represent relative risk ratios derived from 2x2 contingency tables. ^Hazard ratios.

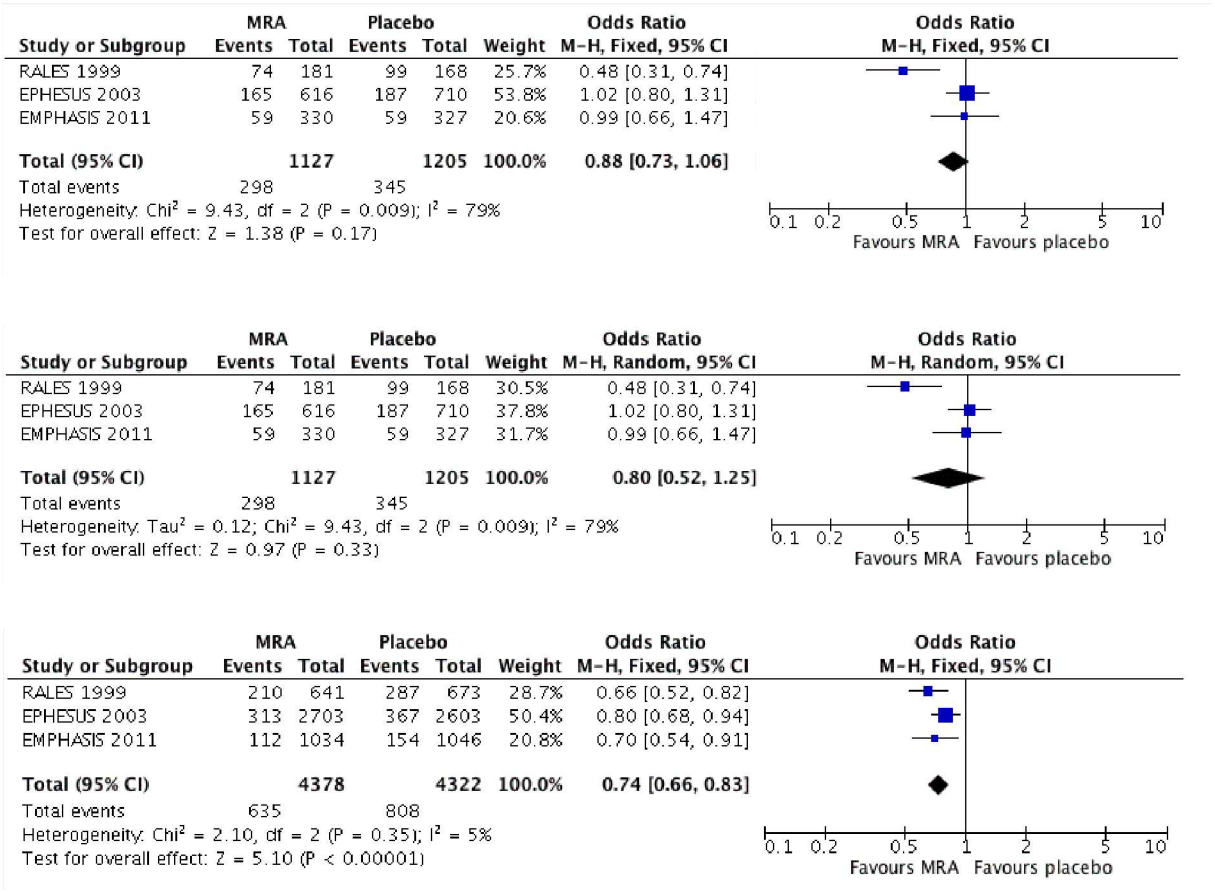

Figure 3. Meta-analysis of mineralocorticoid receptor antagonist treatment on all cause mortality in patients with heart failure and reduced ejection fraction. A: fixed effects model in patients ≥75 years; B random effects model in patients ≥75 years; C fixed effects model in patients <75 years.

Tables

Table 1. Summary of studies

Author, year, trial name	GRADE of evidence	Inclusion Criteria	Study population (N)	Treatment (dose) & duration	Outcomes of interest	Main findings for overall study	Sub-group analysis in elderly patients
Pitt et al, 1999 (RALES)[12]	Moderate[a]	HEFREF: Stable NYHA III/IV LVEF < 35%	Total: 1663 65-74 yrs: 638 ≥75 yrs: 349	Spironolactone (25-50 mg) vs placebo; mean 24 months	All cause mortality	HR 0.70 (0.60-0.82): spironolactone vs placebo (P<0.001)	No treatment interaction for age ≥67 vs <67 years.
Pitt et al, 2003 (EPHESUS)[13]	Moderate[a]	HEFREF: 3-14 days post MI LVEF < 40% Clinical or radiological evidence of HF[b]	Total: 6642 65-74 yrs: 2014 ≥75 yrs: 1328	Epleronone (25 – 50 mg) vs placebo; mean 16 months	i) All cause mortality ii) CV death or CV hospitalisation[c]	i) HR 0.85 (0.75-0.96); ii) HR 0.83 (0.72-0.94): eplerenone vs placebo (P<0.01 for both)	No treatment interaction for age ≥65 vs <65 years for either outcome
Zannad et al, 2011 (EMPHASIS-HF) [14]; Eschalier et al, 2013 (EMPHASIS-HF high risk substudy)[19]	High	HEFREF: Stable HF NYHA II LVEF < 30%[d] BNP>250pg/ml or HF hospitalization in last 12 months	Total: 2737 65-74 yrs: 1197 ≥ 75 yrs: 657	Eplerenone (25 – 50 mg) vs placebo; mean 21 months	CV death or hospitalisation for HF	HR 0.63 (0.54-0.74): eplerenone vs placebo (P<0.0001)	No treatment interaction for age: ≥65 vs <65 years or ≥75 vs <75 years. HR 0.67 (0.49-0.88): eplerenone vs placebo in patients ≥75 years (P<0.0001)
Edelmann et al, 2013 (ALDO-DHF)[16]	Moderate[a]	HEFPEF: Stable NYHA II-III LVEF ≥ 50% Grade ≥1 Diastolic LV dysfunction or AF Peak VO_2 ≤25ml/kg/min	Total: 422 ≥ 67 yrs: 221	Spironolactone 25mg vs placebo; 12 months	Change in VO2 max (ml/min/kg)	No significant treatment effect [+0.1 (-0.6 - +0.8): spironolactone vs placebo (P=0.82)]	+0.15 (-0.8 - +1.10) vs placebo in patients ≥67 years; no treatment interaction for age ≥67 vs <67 years
Pitt et al, 2014 (TOPCAT)[15]	Moderate[a]	HEFPEF: Symptomatic HF LVEF ≥ 45% BNP>100pg/ml[e] or HF hospitalization in last 12 months	Total: 3445 65-74 yrs: 1194 ≥ 75 yrs: 948	Spironolactone (15-45 mg) vs placebo; mean 39 months	CV death, aborted cardiac arrest or hospitalisation for HF	No significant treatment effect. [HR 0.89 (0.77-1.04) spironolactone vs placebo (P=0.14)]	65-74 years: HR 1.01 (0.78-1.31) ≥75 years: HR 0.88 (0.69-1.13) No treatment interaction for age (P=0.36)
Mak et al, 2009 [20].	Moderate[f]	HEFPEF: Symptomatic HF BNP > 100 pg/mL LVEF > 45% Diastolic LV dysfunction	44 (Mean age 80±1.2 years)	Eplerenone (25-50mg) vs placebo; 12 months	Change in MLWHFQ score	No significant treatment effect. [-2 (eplerenone) vs +2 (control); P=NS	N/A
Kurrelmeyer et al, 2014 [21]	Moderate[f]	HEFPEF: NYHA class II-III HF BNP > 62 pg/mL LVEF ≥50% Diastolic LV dysfunction	48 (Mean age 71±1.9 years)	Spironolactone 25mg vs placebo; 6 months	i) Change in 6 min walk (m) ii) Change in KCCQ clinical score	i) +22m (spironolactone) vs +28m (placebo); P=NS ii) +2.3 (spironolactone) vs +7.6 (placebo); P=NS	N/A

HF = heart failure; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; HR = Hazard ratio; MI = myocardial infarction; CV = cardiovascular; BNP = brain natriuretic peptide; AF = atrial fibrillation; MLWHFQ = Minnesota living with heart failure questionnaire; KCCQ = Kansas City cardiomyopathy questionnaire.

[a]Downgraded due to indirectness. [b]Evidence of HF not required in patients with diabetes mellitus. [c]Co-primary endpoints. [d]Or N-terminal pro-BNP ≥500 pg/ml (men) or ≥750 pg/ml (women). [e]Or N-terminal pro-BNP ≥360 pg/ml. [f]Downgraded due to risk of bias

Appendix 3. Medline Search Strategy

1. exp Heart Failure/
2. heart failure*.tw.
3. exp Ventricular Dysfunction/
4. 1 or 2 or 3
5. exp Mineralocorticoid Receptor Antagonists/
6. aldosterone antagonist/
7. mineralocorticoid receptor antagonist*.tw.
8. aldosterone receptor antagonist*.tw.
9. spironolactone/ or spironolactone.mp
10. eplerenone.mp
11. canrenone.mp
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized controlled trials/
16. random allocation/
17. double blind method/
18. single blind method/
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. limit 19 to animal
21. limit 19 to human
22. 20 and 21
23. 20 not 22
24. 19 not 23
25. clinical trial.pt.
26. exp clinical trials/
27. clin$ with trial$.tw.
28. placebos/
29. placebo$.tw.
30. random$.tw.
31. exp research design/
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. limit 32 to animal
34. limit 32 to human
35. 33 and 34
36. 33 not 35
37. 32 not 36
38. comparative study/
39. exp evaluation studies/

40. follow-up studies/
41. prospective studies/
42. (control$ or prospectiv$ or volunteer$).tw.
43. 38 or 39 or 40 or 41 or 42
44. limit 43 to animal
45. limit 43 to human
46. 44 and 45
47. 44 not 46
48. 43 not 47
49. 24 or 37 or 48
50. 4 and 12
51. 49 and 50

Appendix 1

Primary publication	Additional efficacy data and source	Additional safety data and source
Pitt et al, 1999[12]	Number of trial patients aged ≥65 years in each treatment arm[a] Number of patients aged ≥65 years in each treatment arm with primary endpoint (all-cause mortality)[a] Percentage of trial patients aged ≥75 years in each treatment arm.[b] Percentage of patients aged ≥75 years in each treatment arm with primary endpoint[b]	
Pitt et al, 2003[13]	Number of trial patients aged ≥65 years in each treatment arm.[a] Number of patients aged ≥65 years in each treatment arm with[a]: i) all-cause mortality ii) CV death or CV hospitalisation Percentage of trial patients aged ≥75 years in each treatment arm.[c] Percentage of patients aged ≥75 years in each treatment arm with[c]: i) all-cause mortality ii) CV death or CV hospitalisation	Percentage of patients aged ≥75 years in each treatment arm with hyperkalaemia (serum K^+>5.5)[d]
Zannad et al, 2011[14]; Eschalier et al, 2013[19]	Number of patients ≥75 years in each treatment arm with[d]: i) all cause mortality ii) hospitalisation for HF iii) cardiovascular hospitalisation	Number of patients ≥75 years in each treatment arm with[d]: i) hospitalisation for hyperkalaemia ii) hospitalisation for WRF

[a] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-437S002_Inspra_Pharmr.pdf

[b] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21437S002_Inspra_Medr_P4.pdf

[c] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21437S002_Inspra_Medr_P3.pdf

[d] http://db.cbg-meb.nl/Pars/h29963.pdf

Table 2: Safety outcomes in elderly patients

Author, year	Hyperkalaemia (serum K^+>5.5)		Severe hyperkalaemia (serum K^+>6.0)		Hospitalisation for hyperkalaemia		Hospitalisation for WRF	
	MRA	Placebo	MRA	Placebo	MRA	Placebo	MRA	Placebo
Eschalier et al, 2013[19]	40/322* (12.4%)	21/318 (6.6%)	7/322 (2.2%)	4/318 (1.3%)	1/330 (0.3%)	1/327 (0.3%)	5/330 (1.5%)	3/327 (0.9%)
Kurrelmeyer et al. 2014[21]	4/24 (16.7%)	1/24 (4.2%)	3/24 (12.5%)	0/24 (0%)	-	-	-	-
Pitt et al, 2003[13]†	21.5%*	12.7%	-	-	-	-	-	-

MRA = mineralcorticoid receptor antagonist; WRF = worsening renal function.

*P<0.05 for MRA vs Placebo. †absolute numbers not available